PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002849	01.07.2004	02.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D405/14, C07D409/14, C07D213/74, C07D241/20, C07D401/14, C07D401/12

Applicant
BIOFOCUS DISCOVERY LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002849

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002849

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1(part), 8 and 9 (part), 10,11,12-19(part),20

because:

☒ the said international application, or the said claims Nos. 18,19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 10,11,20 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,8,9,12-19 (each part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002849

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6
	No:	Claims	1-4,7-9,12-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9,12-29
Industrial applicability (IA)	Yes:	Claims	1-9,12-17
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002849

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III NON-ESTABLISHMENT

Claims 10, 11 and 20 are completely unclear in scope so that a meaningful examination is not possible (Art. 6 PCT).
Claims 18 and 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
Claim 1 has not been searched. The open definitions 'R1 and R2 are joined to form a ring system' or 'R2 is a C1-C6 optionally substituted alkyl' have produced a large number of potentially novelty destroying compounds. This is also true for the eqivalent definitions of R4 and R5 as well as of R6. The search has thus been restricted to the specific groups mentioned for C1-C6alkyl (eg including ethyl, propyl etc.) and to the ring systems (R1 plus R2 or R4 plus R5) which are defined at pages 5/6 bridging paragraph or page 7, respectively of the description.
The definition 'R2 (and also R5) is optionally linked to the scaffold by a linker ...' has also been ignored because its structure is completely unclear.

IV NON-UNITY

The present application relates to Compounds of Formula (I) and (II). The compounds concerned may be used in the treatment of various diseases such as cancer, cardiovascular diseases, AIDS etc. because of the protein kinase activity. The common structural unit refers to a heteroaromatic six-membered ring including nitrogen as ring atom wherein one meta position is substituted by an amino group. This common feature is, however, already known for compounds in the same technical field. The document WO02/094814 describes kinase inhibitors which may be used in the tratment of cancer, vascular diseases, HIV etc. The experimental part includes several compounds which are 3-amino pyridine derivatives. The present application lacks unity because a common special technical feature which may form the contribution over the prior art does not exist. Hence, the present application consists of the following two inventions according to Rule 13(1) and (2) PCT:

(i) Compounds of formula (I) and related claims (1(part),2,3,6-20(part)
(ii)Compounds of formula (II) and related claims (1(part),4,5,6-20(part).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report
D1: WO 01/17995 A (HUNGATE RANDALL W ; BILODEAU MARK T (US); MANLEY PETER J (US); MERCK &) 15 March 2001 (2001-03-15)
D2: WO 02/24681 A (ORTHO MCNEIL PHARM INC) 28 March 2002 (2002-03-28)
D3: JEANJOT P ET AL: "N-(alkyl)-2-amino-1,4-pyrazine derivatives: Synthesis and antioxidative properties of 3- and 3,5-p-hydroxyphenyl-substituted compounds" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 4, 7 March 2003 (2003-03-07), pages 513-522, XP002287849 ISSN: 0039-7881
D4: WO 01/60816 A (AMGEN INC) 23 August 2001 (2001-08-23)
D1: WO 03/051366 A (ABBOTT LAB) 26 June 2003 (2003-06-26)
D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BOWMAN, R. E. ET AL: "Preparation and cyclization of 3-aza-1,5-diketones" XP002308867 retrieved from STN Database accession no. 1973:29148
D6: WO 03/051366 A (ABBOTT LAB) 26 June 2003 (2003-06-26)
have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 1 and 9 is anticipated by D3. (Article 33(2) PCT). D3 discloses several single compounds covered by the definitions of Claims 1 and 9. See the search report for details.

Most of the definitions are generically covered by Claims 1 of D1 or D2. Due to the very specific definitions, the object of present Claim 1 is, however, considered as a novel selection of D1 and D2.
Furthermore, the object of Claims 1-4,7-9 and 12-19 are considered as anticipated by D6. This documents describes Compounds Ib (page 28) which are exemplified by Examples 123 and 130. The mentioned comounds are disclosed as protein

kinase inhibitors. The subject-matter of Claims 1 and 4 are also anticipated by D5.

3. INVENTIVE STEP

Pyrazines of Formula (I):

Athough D1 and D2 do not mention the Rho kinase inhibiting activity, these documents concern tyrosine kinase activity with overlapping pharmaceutical profile, i.e. cancer treatment. Due to the very close structural relationship (see novelty, above), D1 and D2 should thus be considered as highly relevant in the assessment of inventive step. The application does not include any information of what has been tested. Page 18 gives only a hint to "activity data" but it is not mentioned which activity is measured. With this information, the problem underlying the present application which may be expected as having been solved, can only be seen in the provision of further pyrazine derivatives. The provision of further novel compounds without indication of a technical effect (activity) is per se not inventive and in particular not inventive, i.e. obvious in view of very close structures as disclosed in D1 and D2. Moreover, Claims 12 and 13 indicate that not all of the compounds would have a therapeutic effect but would probably serve only as a tool for identifying active compounds as it is usual in the field of combinatorial chemistry. In this case, Claim 1 would not be inventive, at all for the mentioned reasons.

Pyridines of Formula (II)

Similar observations as made above for the pyrazines (I) hold equally for the pyridines (II). The closest prior art document is to be seen in D6. It should be noted that this group of compounds may be seen as not unitary in itself because an overlapping compound group is already known with the same activity. With the present information, an inventive, i.e. surprising or unexpected effect of compounds structurally very similar to those of D6 is also not detectable.

4. INDUSTRIAL APPLICABILITY

No objection for Claims 1-17 and 20. For the assessment of the present Claims 18

and 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII CERTAIN OBSERVATIONS (CLAIMS)

1. Claims 7 and 8 refer to parts of the description. This is allowable under Art. 6 PCT only in exceptional cases. It is one of the basic requirements of Art. 6 PCT that a claim should be clear in itself.